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EXTENSION OF CENTRAL NERVOUS AND VISUAL SYSTEM OXYGEN TOLERANCE IN PHYSICAL WORK

COMBINED FINAL REPORT

For

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ABSTRACT

This report documents effects of two different patterns of exercise (I-Intermittent and II-Incremental) on two critical aspects of oxygen poisoning (i.e. Central Nervous System and Visual System).

Intermittent Exercise (I)

Multiple physiological functions were monitored in 10 men who performed two 30-minute periods of moderately heavy exercise during 120-minute exposures to oxygen at 2.0 atmospheres in a dry chamber. Both the oxygen dose and exercise workload were similar to or exceeded those experienced in specialized warfare dive profiles.

There were no convulsions, and continuous monitoring of brain electrical activity at rest and during exercise showed no signs of increased excitability. In addition, sequential measurements of peripheral visual fields, pulmonary mechanical function, mental performance, and cardiovascular function during the resting recovery after each of the two 30-minute exercise periods were not detectably altered from pre-exercise control measurements. Pre- and post-exposure measurements of visual acuity, accommodation, pupil diameter, brain visual cortex activity, and retinal electrical activity also revealed no significant differences.

The present finding that 10 men had no symptoms of CNS oxygen toxicity while performing two 30-minute periods of moderate exercise during oxygen exposure at 2.0 ATA appears to differ from the previous observation of Butler and Thalmann (2) that 4 of 40 divers experienced leg twitching near the end of one 30-minute period of underwater exercise at a slightly lower workload during exposure to an oxygen pressure of 2.06 ATA.

Possible reasons for this apparent discrepancy include the following: (1) The present oxygen-exercise exposures were performed in a dry chamber. (2) A group of 10 subjects may not be large enough to detect a 10% incidence of CNS oxygen toxicity. (3) There are indications that an oxygen pressure of 2.0 ATA lies on or near an "asymptote" of CNS oxygen tolerance where a small difference in inspired oxygen pressure will have a relatively large influence on the onset time of toxic effects.

Despite the absence of CNS symptoms in our subjects, elevation of arterial PCO_2 occurred consistently during Type I exercise while breathing oxygen at 2.0 ATA. The operational significance of this finding is that the associated increase in cerebral blood flow will deliver a higher oxygen dose (O_2 flow and PO_2) to the brain and thereby accelerate the occurrence of convulsions. The observed consistency of arterial PCO_2 elevation during exercise, in conjunction with its well documented detrimental influence on CNS oxygen tolerance, led to the

decision to modify the original experiment design by adding a 24-minute sequence of incremental (Type II) exercise in order to provide an opportunity for broader investigation of this phenomenon.

Incremental Exercise (II)

The exposures to 4 levels of incremental exercise while breathing oxygen at 2.0 ATA showed a nearly linear increase in arterial PCO_2 with increasing workload. The magnitude of arterial PCO_2 elevation during exercise varied widely among different subjects. In nearly half of the subjects, the change in arterial PCO_2 at the highest workload was sufficient to have increased cerebral blood flow during exercise by as much as 50% to more than 70% of the resting level. The associated enhancement of cerebral oxygen delivery would be expected to increase oxygen tension prominently in large fractions of brain tissue.

The operational relevance of these results is that they are considered to provide an explanation for part, if not all, of the well established detrimental influence of exercise on CNS oxygen tolerance. It is known that the magnitude of arterial PCO_2 elevation during exercise can be increased by inherent factors such as an individual predisposition to such an effect, as well as by external factors such as the effects of excessive breathing resistance on alveolar ventilation. It is likely that screening procedures could be developed to identify such individuals, and that training procedures in specialized warfare could also be developed to overcome the physiologic tendency to increased arterial PCO_2 during exercise. In addition, recognition that arterial PCO_2 elevation occurs during exercise while breathing oxygen at increased pressures, even under laboratory conditions with minimal breathing resistance, provides a firm basis for the recommendation that all forms of resistance to breathing be kept as low as possible in the use of diving respiratory apparatus.

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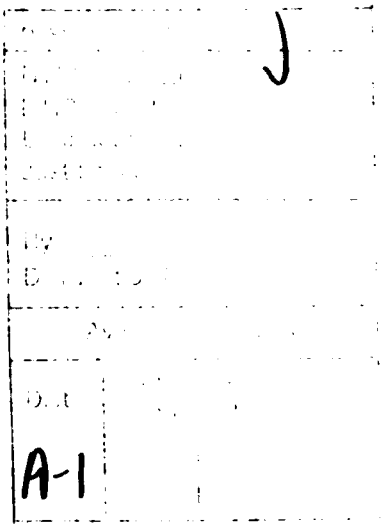

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INTRODUCTION

Adverse effects of exercise on central nervous system oxygen tolerance in man are well known and have been demonstrated repeatedly in working divers (1-4). These effects are manifested most prominently by the occurrence of oxygen convulsions at shorter exposure times or at lower oxygen pressures than those found in men at rest. Although it is probable that the development of CNS oxygen toxicity is generally accelerated in all individuals by effects of concurrent exercise, there are indications that some men are unusually susceptible to the occurrence of oxygen convulsions during exercise (1,2). The causes of this phenomenon have not been established over the more than 40 years since its recognition, and it has not been practical to identify susceptible individuals in advance.

Most previous studies of exercise effects on CNS oxygen tolerance have focused on occurrence of signs and symptoms with almost no emphasis on objective physiologic measurements (1-4). It is conceivable that oxygen-exercise interactions are associated with measurable changes that may provide some clue regarding possible causes of accelerated convulsions, or some means to identify unusually susceptible individuals in advance. There are indications that hyperoxic impairment of peripheral vision may also be accelerated by concurrent exercise (5).

These two related Projects were designed to investigate such possibilities in parallel, by making objective measurements of central nervous system and visual responses to oxygen-exercise exposure at 2.0 ATA, along with concurrent measurements of ventilatory, temperature, pulmonary, and cardiac responses. Emphasis was placed upon the measurement of indices that were found to be altered during the earlier, continuous hyperoxic exposures of men at rest (Predictive Studies V) (6-9), carried out in this laboratory with Naval support. Results of the two Projects (Central Nervous System and Visual System O_2 Tolerance), which were closely integrated in both design and performance, have been combined in a single report to facilitate interpretation and application of this information.

Intermittent hyperoxia deferral. An early overall objective of the 2 related Projects was the development of effective patterns of alternating hyperoxic and normoxic exposure periods to extend both central nervous system and visual system oxygen tolerance during operational working dives at an ambient pressure of 2.0 ATA. When no evidence of either central nervous system or visual manifestations of oxygen toxicity could be detected during the initial exposures to the selected rigorous conditions of oxygen pressure and exercise workload, the development of intermittent O_2 exposure patterns for effective extension of CNS and visual oxygen tolerance became impractical. The absence of a reliable, preconvulsive index of CNS or visual

oxygen toxicity was an absolute handicap to investigation of intermittent hyperoxia as a practical means of oxygen tolerance extension during working dives.

However, the observation of consistent elevations in arterial PCO_2 during exercise while breathing oxygen at 2.0 ATA provided an objective physiological alteration that could be monitored. By virtue of its known influence on brain blood flow and oxygen dose (10,11), this alteration is highly relevant to development of CNS oxygen poisoning even in the absence of convulsions. Accordingly, the original experiment purpose was modified to incorporate, as a primary focus of investigation, the evaluation of degree and possible causes of arterial PCO_2 elevation during two forms of oxygen-exercise exposure at 2.0 ATA.

METHODS

After a period of medical evaluation and training, which included individual determinations of exercise tolerance, each of 10 subjects performed a 120-minute period of intermittent exercise in which 30-minute work cycles were alternated with 30-minute rest and measurement cycles during air breathing at 1.0 ATA (Type I Exercise). Control measurements of central nervous system, visual, ventilatory, temperature, pulmonary, and cardiac responses were obtained before, during, and after the intermittent exercise period. At a later date, the same measurement sequence was performed before, during, and after the same intermittent exercise profile during oxygen breathing at 2.0 ATA. In 9 of the 10 subjects, a similar scope of measurements was performed before, during, and after a different exercise protocol which consisted of 4 consecutive 6-minute periods of incremental exercise workload during oxygen breathing at 2.0 ATA (Type II Exercise).

Oxygen was administered in each series by facemask, inside a recompression chamber large enough to accomodate the subject, bicycle ergometer (W.E.Collins Models Pedalmode or Pedalmate), two investigators, and required instrumentation. Additional details describing the chamber system are available (12).

Subjects

Each subject received a comprehensive medical evaluation which included a medical history and physical examination, neuro-ophthalmologic evaluation, electrocardiogram, electroencephalogram, electroretinogram, visual acuity and fields, chest x-ray, urinalysis, and hematology profile. Informed consent was obtained on 2 separate occasions prior to oxygen-exercise exposure at 2.0 ATA. All procedures and measurements were approved by the Human Studies Committee of the University of Pennsylvania.

The fitness and exercise capability levels of each subject were evaluated by measuring ventilatory and gas exchange responses to graded exercise on the bicycle ergometer in 2 separate trials. Average results of both trials for each subject are plotted as individual relationships of oxygen uptake to ergometer workload in Appendix Figure 1. Average maximum oxygen uptake in the supine position for all 10 subjects was 4.18 liters per minute (L/min) or 50 milliliters (ml) per kilogram at an average ergometer workload of 245 watts.

Alternating Work and Rest Profile (Type I Exercise)

The average data for each subject were used to select an individual workload of about 60% of maximum, to be used during subsequent air control and oxygen exposure measurements for

alternating work and rest exposures. The intent was to provide an average workload intensity of nearly 2.0 L/min to equal or exceed workloads measured previously in underwater swimmers (1,2) and in previous studies of oxygen-exercise interactions (13). When sustained over a 30-minute period and then repeated, the selected ergometer workload, which had an average value of 150 watts for all 10 subjects, represented prominent exercise stress that could be performed only by fit individuals.

Measurements. The measurement sequences that were performed before, during, and after the 120-minute period of intermittent exercise while breathing oxygen at 2.0 ATA are summarized in Appendix Figure 2. Visual evoked responses, visual acuity, accommodation, pupilometry, and electroretinography were measured at 1.0 ATA before and after the oxygen-exercise exposure at 2.0 ATA. During oxygen exposure at 2.0 ATA, pulmonary ventilation, deep body temperature, end-tidal (alveolar) P_{CO_2}, and mask oxygen concentration were monitored continuously at rest and during exercise. Brain electrical activity was also monitored continuously, but the indicated times represent periods of total relaxation to ensure a good record. Visual fields, pulmonary function, and mental performance were evaluated at rest while breathing oxygen before and after the first exercise period and while breathing air at 2.0 ATA after the second exercise period. Cardiovascular function, rate of CO_2 elimination, and arterial blood gases were monitored during each rest and exercise period at 2.0 ATA.

Control measurements obtained during air breathing at 1.0 ATA were identical to those shown in Appendix Figure 1 with a few exceptions. Visual evoked responses, brain electrical activity, arterial blood gases, and arterial pressure were not monitored at 1.0 ATA. During air breathing at 1.0 ATA, the rate of O_2 uptake was measured concurrently with rate of CO_2 elimination. Of the parameters that were monitored continuously at 2.0 ATA, only rectal temperature was measured at 1.0 ATA.

Incremental Exercise Profile (Type II Exercise)

The measurement sequences that were performed before, during, and after the 24-minute period of incremental degrees of exercise while breathing oxygen at 2.0 ATA are summarized in Appendix Figure 3. The major difference between this profile and that described in Appendix Figure 2 is that four consecutive, 6-minute periods of incremental work at ergometer workloads of 50, 100, 150, and 200 watts replace the two 30-minute periods at an average workload of 150 watts that were used in the intermittent exercise profile. The 24-minute period of continuous, incremental exercise is preceded and followed by 30-minute periods of oxygen breathing at rest. Arterial blood gases were also measured at rest during 10-minute periods of normoxia at 2.0 ATA before and after the 84-minute oxygen exposure.

Gas Administration System

Oxygen from a liquid source was humidified by bubbling through water (80% relative humidity) and delivered to a 30-liter storage bag. Inspired O_2 from the bag was conducted via 1.5-inch i.d. tubing to an exercise test mask (Hans Rudolph #7900M) with rated inspiratory and expiratory resistances at 600 liters/min of 6.2 and 4.8 cm H_2O, respectively. Expired gas was conducted via 1.5-inch i.d. tubing to a collection bag and "dumped" overboard, except when it was collected in a weather balloon for respiratory measurements.

Central Nervous System Function

Electroencephalography. Twelve channels of EEG were continuously recorded from 12 scalp electrodes onto a Grass Model 8-16 EEG machine and onto a magnetic tape recorder. A modified INT 10-20 system was used for electrode placement.

Mental performance. Mental and psychomotor function were evaluated before and after each period of exercise. Specific tests that were used included a visual digit span test of short term memory ability, a key insertion test of finger dexterity ability, an operations test of number facility and general reasoning abilities, and a visual reaction time test of response speed ability. This sequence of four consecutive tests was administered and scored over a 7-min period by computer as a component of the Institute-developed Performance Measurement System (14).

Visual Function

Electroretinography. The electroretinogram (ERG) was obtained from the dark adapted (right) eye, using a Burian-Allen electrode that rested on a soft contact lens to prevent corneal abrasion. The retinal response was elicited by a 10-microsecond flash stimulus from a Grass Model PS22 Photostimulator outside the chamber. A specially modified (sealed and purged with nitrogen) photoflash tube inside the chamber was mounted onto a standard Ganzfeld apparatus. Visual stimuli consisted of three different intensities of blue light and one intensity of red light. The largest b-wave amplitude obtained in two or three trials was recorded for each intensity.

After magnification by a Grass Model P511 Amplifier, the electrical signal from the ERG electrode was recorded and stored within the memory of a Hewlett-Packard Model 3561A Signal Analyzer. Hard Copy of the ERG trace was obtained with a Hewlett-Packard Model 2671-G Graphic Printer.

Perimetry. Peripheral visual field measurements were made monocularly on the light adapted (left) eye with the right eye

patched. Perimetric fields were plotted every 30° on a Rodenstock Projection Perimeter using the 1.12 mm test spot. Field luminance of the hemisphere was fixed at 0.50 log mL, while luminance of the test spot was maintained at 2.0 log mL. All external chamber lights were turned off during the period of visual field measurement. Maintenance of proper fixation was assured throughout each period of measurement by frequent monitoring with the viewing device built into the perimeter. The stimulus was presented randomly in any of the 12 selected field locations, with each presentation being from the "not seen" to the "seen" mode. Responses to two complete sets of presentations were averaged for each visual field measurement.

Visual evoked cortical responses. The pattern reversal visual evoked cortical response (VER) was obtained with a Medical Systems Corporation Model D112 Pattern Reversal Stimulator outside the chamber projecting onto a rear projection screen inside the chamber via a viewport. The subject was seated with his eye at a distance of one meter from the screen. The signal from the scalp EEG electrodes (F_Z/O_Z) was magnified by a Grass P511 Amplifier and sent to a Hewlett-Packard 3561A Signal Analyzer for signal averaging and recording (2671-G Graphic Printer).

Visual acuity. Central visual acuity was measured with the test chart on a modified MacBeth illuminator stand. The subject was seated in front of the chart with his eye position maintained at a fixed distance of 35 cm from the chart surface by a restraining device which rested on the bridge of his nose and cheekbones. The chart was viewed under the illumination of the MacBeth source which provided 0.95 log lux illuminance (approximately equivalent to average daylight). Visual acuity of the left eye was measured with the right eye patched.

Accommodation. The closest distance at which the subject could accommodate was measured with a modified Adler Near-Point Rule. A fine-letter target attached to a millimeter rule was initially positioned to be in sharp focus for the left eye with the right eye patched. It was then moved slowly toward the eye while the subject actively accommodated to the decreasing distance until blurring began at the near-point. Accommodative near-point was measured as the average of at least 5 readings. All trials were performed with chamber lights on full brightness.

Pupilometry. Diameter of the left pupil was estimated to the nearest 0.5 mm by matching pupil size with a range of similar test circles on a standard chart. This determination was made with chamber lights on full brightness while the subject looked directly at the light.

Ventilation and Gas Exchange

During oxygen breathing at 2.0 ATA, inspiratory flow and pattern of ventilation were measured with a pneumotachygraph (Fleisch #4) on the inspiratory side of the gas administration system. These measurements were supplemented with timed collections of expired gas in a large weather balloon which was then evacuated to 1.0 ATA for measurement of volume in a wet test gasometer. Mean expired CO_2 concentration was also measured at 1.0 ATA with a Datex Model CD-101 Infrared CO_2 Analyzer.

Arterial Blood Gases

Arterial blood was sampled anaerobically into precision-bored glass syringes by standard procedures. Analyses for pH, P_{CO_2}, and P_{O_2} were performed in duplicate with a Corning Model 165 Blood Gas Analyzer electrode block especially adapted for use inside the chamber.

Body Temperature

Rectal temperature was recorded continuously. The temperature sensor was a Yellow Springs 400 series probe with a Model 46 thermistor thermometer and a range of 35 to 45°C.

Pulmonary Function

Automated flow volume loops inside and outside the chamber were obtained with "dry sealed" spirometers (Ohio Medical Products Models 827 and 840) and Vacumetrics Inc. software. Carbon monoxide diffusing capacity of the lung was measured with a W. E. Collins Inc. Modular Lung Analyzer. Airway resistance, pulmonary compliance, and functional residual capacity were measured using a W. E. Collins Inc. Body Plethysmograph.

Cardiovascular Function

Electrocardiogram. The ECG was monitored continuously on a Siemens Corporation Model Sirecust 400 Clinical Monitor and recorded onto magnetic tape and a Holter Monitor.

Cardiac output. Cardiac stroke volume was measured with the aid of a Minnesota Impedance Cardiograph (Instrumentation For Medicine Inc. Model 304A) whose output was recorded onto a Honeywell Visicorder (906B) and onto magnetic tape. Cardiac output was calculated as the product of heart rate and stroke volume.

Blood pressure. Blood pressure was measured via an indwelling arterial catheter using a disposable blood-pressure transducer (Abbott Critical Care Systems) coupled to the Siemens

Patient Monitor. The pulse waveform was recorded onto a Visicorder Oscillograph.

Orthostatic maneuver. An orthostatic maneuver was obtained at selected intervals by having the subject arise from the prone position to the standing position in a rapid but controlled maneuver. The EKG, beat-by-beat heart rate, blood pressure, and cardiac stroke volume were simultaneously recorded onto the Visicorder Oscillograph before, during, and after the orthostatic maneuver.

Statistical Analysis

Means and standard deviations for each measurement parameter and experimental condition are summarized in appendix data tables. Average values include all subjects for whom data are available. In some cases, it was not possible to obtain data for all subjects in each condition. For statistical comparisons of average values for different conditions, analyses across a range of conditions were performed with data only from the same subjects. All tests were made at the 5% level, with critical values adjusted for multiple comparisons where required.

Analysis of variance techniques were applied to all data except the measurements of visual function. One-way ANOVA with repeated measures was used where the comparisons of interest were within an individual experimental protocol. ANOVA for two factors with repeated measures was used to determine whether responses to two 30-minute periods of exercise were the same for air at 1.0 ATA and oxygen at 2.0 ATA. Overall main effects were tested for each variable, followed by comparisons between the two oxygen pressures at each exercise level, even where the overall effect was not significant. These individual comparisons are designated in relevant appendix data tables.

The effects of the incremental exercise protocol were assessed by testing for linear and quadratic trends across the resting and four exercise levels. The quadratic trend suggested a plateauing at the high work levels.

Paired t-tests were performed on the measurements of visual function which were made at 1.0 ATA before and after both the air control exposures at 1.0 ATA and the oxygen-exercise exposures at 2.0 ATA. They were also used for the visual field measurements obtained before and after each exercise period at 2.0 ATA.

RESULTS

Average results of control measurements obtained during performance of the alternating work and rest profile (Appendix Figure 2) while breathing air at 1.0 ATA are summarized in Appendix Tables 1-5. Average responses to the same profile during oxygen exposure at 2.0 ATA are summarized in Appendix Tables 6-11. Average responses to the incremental exercise profile (Appendix Figure 3) during oxygen exposure at 2.0 ATA are summarized in Appendix Tables 12-17. Statistical analyses of selected data are summarized in Appendix Tables 18-21.

Effects on Brain Electrical Activity

Examples of electroencephalographic recordings obtained at rest and during exercise at 2.0 ATA are shown in Appendix Figures 4a and 4b. These records demonstrate that technical quality of the electroencephalogram can be maintained in a supine subject who is pedalling a bicycle ergometer. Online inspection of the EEG records during each oxygen-exercise exposure revealed no evident abnormalities at rest or during exercise. Detailed analysis of the EEG records will be completed when appropriate computer algorithms for frequency spectrum analysis have been developed.

Effects on Mental and Psychomotor Performance

Average results of mental function testing are summarized in Appendix Tables 1, 6, and 12. Average scores for each of the administered tests are very similar before and after each 30-minute period of exercise for both the control measurements obtained while breathing air at 1.0 ATA (Appendix Table 1) and the corresponding measurements obtained before, during, and after oxygen exposure at 2.0 ATA (Appendix Table 6). Scores obtained before and after 24 minutes of incremental exercise while breathing oxygen at 2.0 ATA are also similar (Appendix Table 12). The performance data indicate that short term memory, manual dexterity, number facility, reasoning ability, and response speed are maintained under all tested conditions of exercise and oxygen exposure.

Effects on Visual Function

Control measurements of visual function obtained before and after exercise while breathing air at 1.0 ATA are summarized in Appendix Table 2. Measurements obtained after two 30-minute periods of exercise during oxygen exposure at 2.0 ATA are contained in Appendix Table 7 and corresponding measurements obtained after 24 minutes of incremental exercise while breathing oxygen at 2.0 ATA are listed in Appendix Table 13.

Most of the average values of visual function parameters measured before and after oxygen-exercise exposure are nearly identical. In those instances where average values before and after oxygen exposure are slightly different, the differences are well within the range of random variability and are not statistically significant.

Overall, the measurements of visual function indicate that neither of the 2 oxygen-exercise protocols at 2.0 ATA had any effect on visual acuity, near-point accommodation, or pupil diameter. Peripheral vision was fully maintained, and there were no detectable changes either in retinal electrical activity or in visual evoked cortical responses.

It is of interest that the only significant changes that were observed in this series of experiments were found during the air breathing control exposures at 1.0 ATA. The retinal electrical responses to three different intensities of blue light were consistently and significantly reduced after two 30-minute periods of exercise. Average responses to the intermediate intensity are shown in Appendix Table 2. The average magnitude of decrement in ERG b-wave amplitude, which ranged from 6.1% to 8.8% of the pre-exercise control values, was quantitatively small and of unknown origin. There were no similar changes after two 30-minute periods of exercise while breathing oxygen at 2.0 ATA.

Effects on Pulmonary Function

Flow-volume loops were performed during each rest or recovery period before and after each period of exercise. Average values of forced vital capacity (FVC), one-second forced expired volume (FEV_1), peak expiratory flow rate (PEFR), and maximal mid-expiratory flow rate (FEF_{25-75}) are listed in Appendix Tables 3, 8, and 14. Average FVC and FEV_1 either remain essentially unchanged or are slightly increased after each period of exercise. The FVC increments are statistically significant after both 30-minute periods of exercise while breathing oxygen at 2.0 ATA. The increments in FEV_1 are significant after the first exercise period at 1.0 ATA and after the second exercise period at 2.0 ATA.

Average PEFR and FEF_{25-75} are also unchanged or slightly increased except for a small decrement in PEFR after 24 minutes of incremental exercise during oxygen exposure at 2.0 ATA. None of the changes in PEFR are statistically significant, and FEF_{25-75} is significantly increased only after the second 30-minute exercise period during oxygen exposure at 2.0 ATA (Appendix Table 8).

The data show that pulmonary mechanical function is either not changed or is slightly improved by exercise even when combined with oxygen exposure at 2.0 ATA. Previous studies have

also shown that some components of pulmonary function are improved after a period of prolonged exercise, presumably as a result of exercise-induced bronchodilatation (15,16).

Effects on Pulmonary Ventilation and Gas Exchange

Pulmonary ventilation and gas exchange were measured before, during, and after each period of exercise. Average measurements for the same 10 subjects who performed the same ergometer workloads at 1.0 ATA while breathing air and, on a subsequent day, at 2.0 ATA while breathing oxygen are summarized in Appendix Tables 4 and 9, respectively.

Rate and pattern of ventilation. During oxygen breathing at 2.0 ATA, ventilation increased from 9.41 L/min at rest to 52.44 L/min during the first exercise period, decreased to 11.05 L/min during the subsequent recovery period, and increased to 51.96 L/min during the second period of exercise (Appendix Table 9). Corresponding rates of ventilation for the same 10 subjects during air control exposures at 1.0 ATA were 8.98 L/min at rest, 54.56 L/min for the first exercise period, and 54.23 L/min for the second period of exercise (Appendix Table 4).

Average values for the 7 subjects in whom data were obtained at all measurement points during air breathing at 1.0 ATA and oxygen breathing at 2.0 ATA were compared statistically by analysis of variance (Appendix Table 18). Although corresponding average values for total ventilation at 1.0 and 2.0 ATA were similar at rest and during exercise, there were significant differences in the pattern of breathing. During oxygen breathing at 2.0 ATA, average values of tidal volume were significantly larger at rest, during both exercise periods, and during both recovery periods. Corresponding values of breathing frequency were significantly lower at 2.0 ATA only during the second 30-minute period of exercise.

When incremental exercise was performed during oxygen breathing at 2.0 ATA, average ventilatory responses of 9 subjects to ergometer workloads of 50, 100, 150, and 200 watts were 26.44, 36.66, 52.09, and 75.60 L/min, respectively (Appendix Table 15). Since 3 subjects could not complete the 200-watt workload, average ventilatory responses for the 6 subjects who completed all 4 workloads are shown in Appendix Table 19 along with analysis of variance results. The increased levels of ventilation were achieved by progressive increments in both tidal volume and breathing rate.

The data in Appendix Table 15 also indicate that average ventilation at rest increased significantly from 7.91 L/min on a normoxic inspired gas at 2.0 ATA to 9.79 L/min on oxygen prior to starting exercise. A similar significant change in resting ventilation at 2.0 ATA from 8.12 L/min on chamber air to 9.56

L/min on oxygen was observed in 7 subjects before starting the first of two 30-minute exercise periods. Average breathing frequency increased significantly from 14 to 16 breaths/min in the same subjects.

Oxygen uptake and carbon dioxide elimination rates. Average rates of oxygen uptake in 10 subjects during the first and second exercise periods while breathing air at 1.0 ATA were 1.868 and 1.873 L/min, respectively (Appendix Table 4). Corresponding rates of carbon dioxide elimination were 1.841 and 1.817 L/min. During oxygen breathing at 2.0 ATA, CO_2 elimination rates for 2 periods of exercise at the same ergometer workload were 1.802 and 1.734 L/min (Appendix Table 9). For the 7 subjects in whom all measurements were obtained at both 1.0 and 2.0 ATA, the average rate of CO_2 elimination for the second 30-minute exercise period was reduced significantly by analysis of variance from 1.878 L/min during air breathing at 1.0 ATA to 1.719 L/min during oxygen breathing at 2.0 ATA (Appendix Table 18). The reduced rate of CO_2 elimination for the same workload during oxygen breathing could be explained by a decreased level of metabolic acidosis with a corresponding reduction in bicarbonate buffering of hydrogen ions.

Arterial blood gases. Average values of arterial PO_2, PCO_2, pH, and $[HCO_3^-]$ measured before, during, and after two 30-minute periods of oxygen-exercise exposure at 2.0 ATA are summarized in Appendix Table 10. Average arterial PCO_2 during oxygen breathing at 2.0 ATA rose from a resting value of 38.1 mm Hg to 43.3 mm Hg for the first work period, fell to 38.3 mm Hg for the first recovery period, and rose to 42.8 mm Hg for the second work period. Both increments in arterial PCO_2 during exercise were statistically significant. Individual changes in arterial PCO_2 during exercise ranged from -0.2 to 10.8 mm Hg in different subjects. Average arterial pH on oxygen at 2.0 ATA was 7.422 at rest, decreased significantly to 7.347 during exercise, rose to 7.410 during the following recovery period, and again decreased significantly to 7.372 during the second work period.

Appendix Table 16 summarizes average values of arterial PO_2, PCO_2, pH, and $[HCO_3^-]$ for the 9 subjects who had oxygen-exercise exposures at 2.0 ATA while attempting to perform 4 consecutive 6-minute periods of exercise at ergometer workloads of 50, 100, 150, and 200 watts. Three of the 9 subjects were unable to complete the highest workload. Average arterial PCO_2 values during oxygen breathing at 2.0 ATA for the 6 subjects who performed all 4 workloads increased significantly from 34.3 mm Hg at rest to 36.8, 38.9, 41.6, and 44.0 mm Hg, respectively, at the 4 incremental workloads (Appendix Table 20). Corresponding values of arterial pH decreased significantly from 7.434 at rest to 7.418, 7.400, 7.380, and 7.346 at the incremental workloads.

Individual values of arterial PCO_2 for the 6 subjects who completed all 4 workloads are shown in Appendix Figure 5. Measurements were made before, during, and after exercise in the sequence plotted on the graph. Prior to the start of exercise, the consistent decrement in arterial PCO_2 during the transition from normoxia to oxygen breathing at 2.0 ATA is associated with a concurrent increment in ventilation (Appendix Table 15). The reverse transition after termination of exercise is associated with an elevation in PCO_2 in 5 of the 6 subjects. During the period of incremental exercise, all 6 subjects had progressive elevations in arterial PCO_2 as workload was increased. Arterial PCO_2 increments in individual subjects ranged from 4.4 to 14.2 mm Hg at the highest workload.

Average values of arterial PCO_2 and pH in the same 6 subjects are plotted against corresponding rates of CO_2 elimination as an index of workload during oxygen breathing at 2.0 ATA (Appendix Figures 6 and 7). The data show a nearly linear increase in arterial PCO_2 with a similar decline in arterial pH as workload is increased.

Effects on Cardiovascular Function

Cardiovascular parameters including heart rate, stroke volume, cardiac output, and arterial blood pressure were measured before, during, and after each period of exercise at 1.0 and 2.0 ATA. Average values are summarized in Appendix Tables 5, 11, and 17. Average values of deep body temperature are included in the same tables. Average values of heart rate, stroke volume, and cardiac output measured at 1.0 and 2.0 ATA in the same subjects are compared statistically in Appendix Table 21.

All changes in deep body temperature and both systolic and diastolic blood pressure were appropriate for the corresponding level of exercise and did not appear to be significantly influenced by ambient pressure or inspired PO_2 (Appendix Tables 5 and 11).

Average values of stroke volume were consistently higher at 2.0 ATA, but the difference was statistically significant only for the second recovery period (Appendix Table 21). Average heart rates were consistently lower during oxygen breathing at 2.0 ATA. From a resting value of 55 beats/minute, heart rate increased to 129 during the first exercise period, fell to 61 during the first recovery period, rose to 135 for the second exercise period, and returned to 61 during the subsequent recovery period. Corresponding control values for air breathing at 1.0 ATA were 59, 145, 76, 151, and 78 beats/minute, respectively. All differences were statistically significant except for the pre-exercise resting control value. Average cardiac output responses to 30-minute periods of exercise were

slightly lower at 2.0 ATA, but the differences were not significant.

Cardiac responses to incremental exercise during oxygen exposure at 2.0 ATA (Appendix Table 17) were characterized by a progressive increase in heart rate with a parallel decrement in stroke volume. Both trends were linear and statistically significant. Average heart rate increased from a resting value of 49 to 140 beats/minute at the highest workload, while the corresponding values of stroke volume declined from 164 to 114 ml. Cardiac output rose progressively and significantly at workloads of 50, 100, and 150 watts and then plateaued during the 6-minute work period at 200 watts, which approached the maximum workload (3 minutes at 245 watts) for these subjects during air breathing at 1.0 ATA (Appendix Figure 1). Blood pressure and body temperature also increased significantly during incremental exercise at 2.0 ATA (Appendix Table 17).

DISCUSSION

Oxygen exposures at 2.0 ATA for a total duration of 120 minutes with two 30-minute periods of moderately heavy exercise have been completed in 10 subjects with no detectable impairment of visual function or decrements in mental and psychomotor performance. There were no indications of incipient convulsions or other manifestations of central nervous system oxygen toxicity. Continuous monitoring of the electroencephalogram at rest and during exercise showed no signs of increased neuronal excitability. In addition, repeated measurements of ventilatory and cardiovascular responses, both at rest and during exercise, and of pulmonary mechanical function during the resting recovery after each of the two 30-minute exercise periods revealed none of the toxic effects that were observed during the prolonged resting exposures of Predictive Studies V (7-9,17).

Comparison of Present Results with Previous Studies of Exercise Effects on Central Nervous System Oxygen Tolerance

Many previous studies have demonstrated adverse effects of exercise on central nervous system oxygen tolerance in man (1-4). Of these studies, the carefully documented and relatively recent observations of Butler and Thalmann (1,2) are most appropriate for comparison with our results. In a study that included a total of 465 man-dives on 14 different experiment profiles, these investigators (2) had 37 divers perform intermittent exercise alternating 6 minutes of work with 4 minutes at rest (average oxygen uptake of 1.29 L/min) during 90-minute exposures to oxygen at 30 fsw (1.91 ATA). No symptoms were experienced by 33 of the 37 divers, but 1 convulsed at 82 minutes (3 concurrent exposures were stopped at 82 minutes prior to onset of symptoms). In another series of experiments on a different profile, 40 man-dives were carried out at 35 fsw (2.06 ATA) with 30 minutes of continuous exercise at a workload of 1.66 L/min. Four divers developed leg twitching at 25 to 29.5 minutes of exposure to give a 10% incidence of definite CNS symptoms.

There are several possible explanations for the apparent discrepancy between the above-cited observation of Butler and Thalmann that 30 minutes of exercise at a workload of 1.66 L/min and an inspired oxygen pressure of 2.06 ATA produced a 10% incidence of CNS oxygen toxicity and the present observation that no detectable effects of CNS toxicity occurred in 10 subjects who performed two 30-minute periods of exercise at a workload of 1.80 L/min while breathing oxygen at 2.0 ATA for 120 minutes. It is possible that a group of 10 subjects is too small to detect a 10% incidence of CNS oxygen toxicity. In addition, there are indications that an oxygen pressure of 2.0 ATA lies near or on an "asymptote" of CNS oxygen tolerance (18) where small differences in inspired PO_2 will have relatively large influences on onset times of toxic effects. Another difference between the two

studies, which may be important, is that the divers investigated by Butler and Thalmann worked underwater, while the subjects studied in this Project performed exercise in a dry chamber. Plans for direct investigation of individual differences in responses to oxygen-exercise exposure at 2.0 ATA in a dry chamber and during immersion underwater in the same subjects are discussed below.

Ventilatory Responses to Hyperoxia at Rest and during Exercise

When oxygen is breathed at 2.0 ATA, each 100 ml of arterial blood contains about 4.4 ml of oxygen as compared to only 0.3 ml during air breathing at 1.0 ATA (19). As a result of this increased volume of physically dissolved oxygen, less oxygen is removed from hemoglobin which in turn becomes less able to bind carbon dioxide. The decrement in hemoglobin-bound CO_2 is associated with a corresponding increment in physically dissolved CO_2 and concurrent increments in tissue PCO_2 and $[H^+]$. The subsequent stimulation of central respiratory chemoreceptors is partially opposed by a concurrent, oxygen-induced depression of peripheral chemoreceptors (19). Once a steady-state has been achieved, the net effect is a mild level of hyperventilation that persists even when the oxygen exposure is continued for several hours (8).

Although the net ventilatory stimulation and arterial hypocapnia induced by hyperoxia are readily evident at resting levels of ventilation, ventilatory responses to exercise during oxygen breathing at 2.0 ATA are such that arterial PCO_2 rises nearly linearly with increasing workload (Appendix Figure 6). This pattern differs from the corresponding relationship of arterial PCO_2 to incremental exercise during air breathing at 1.0 ATA, where endurance-trained athletes typically have a slight increase in arterial PCO_2 at low workloads followed by a progressive fall at higher workloads (20). The multiple influences that contribute to this difference include the greater work of breathing caused by increased gas density at 2.0 ATA (21) and the reduced level of metabolic acidosis associated with oxygen breathing at 2.0 ATA (13). It is also possible that the balance between central stimulant and peripheral depressant influences of hyperoxia is different during exercise than at rest.

Hypercapnia Influences on Oxygen Tolerance

The operational significance of arterial PCO_2 elevation during oxygen breathing is that the associated increase in cerebral blood flow will deliver a higher oxygen dose to the brain (19,22). The potential importance of this finding, which became evident during the initial oxygen-exercise exposures at 2.0 ATA, led to the decision to modify the original experiment design by substituting broader investigation of arterial PCO_2

elevation during exercise for previously planned normoxic control exposures at 2.0 ATA.

Lambertsen et al (13) have also considered possible influences of hypercapnia on tolerance to oxygen-exercise exposure in man. These investigators made extensive measurements in 6 subjects of physiological responses to 23 minutes of exercise at an average workload of 1.90 L/min while breathing air at 1.0 ATA and, on the same day after a 60-minute rest period, during oxygen exposure at 2.0 ATA. Average arterial PCO_2 during exercise on oxygen was 3.6 mm Hg higher than for the same workload on air at 1.0 ATA. Although a small measured increment in cerebral blood flow of 3.3 ml of blood per 100 grams of brain per minute was not statistically significant, the authors pointed out that the concurrent measurement of a significant decrement in the arterio-venous oxygen content difference across the brain may well have reflected an increase in cerebral blood flow that was not detected by the method of direct measurement that was then available. The authors also concluded that subjects who develop hypercapnia during exercise on oxygen at 2.0 ATA would probably have an exaggerated increase in mean brain capillary PO_2.

Results of the present study indicate that elevation of arterial PCO_2 during oxygen-exercise exposure at 2.0 ATA could contribute to an accelerated onset of CNS oxygen toxicity under such conditions (Appendix Tables 10 and 16). In the transition from rest to the first 30-minute exercise period, arterial PCO_2 rose in all 10 subjects for an average change of 5.2 mm Hg, with individual increments as great as 9.8 mm Hg (Appendix Table 10). Direct measurements of cerebral blood flow in normal resting men with arterial PCO_2 values ranging from 20 to 60 mm Hg indicate that this relationship can be approximated by an asymmetrical sigmoid curve (11) on which each 1 mm Hg rise in arterial PCO_2 within the normal range increases cerebral blood flow by an amount that varies from about 2.5% (11) to nearly 5% (10) in different series of experiments. If the normal relationship of cerebral blood flow to arterial PCO_2 is maintained during exercise, an arterial PCO_2 elevation of 5.2 mm Hg would increase cerebral blood flow by at least 13% to as much as 26%.

The observation of arterial PCO_2 elevation during oxygen-exercise exposure at 2.0 ATA was confirmed and extended by measuring arterial PCO_2 in 9 subjects who performed 4 consecutive 6-minute periods of incremental work while breathing oxygen at 2.0 ATA (Appendix Table 16, Appendix Figures 5 and 6). In the 6 subjects who completed all 4 workloads, average arterial PCO_2 rose by 9.7 mm Hg at the highest workload, with individual increments as great as 14.2 mm Hg. Assuming that the normal relationship of cerebral blood flow to arterial PCO_2 persists during exercise, cerebral blood flow would increase by about 24% to 48% on the average, with individual increments as great as 36% to over 70%. Cerebral venous and mean brain capillary PO_2 would

be expected to increase prominently in response to such increments in cerebral blood flow.

Although direct measurements of cerebral venous PO_2 under such conditions are not available, the order of magnitude of PO_2 elevation can be approximated from measurements of arterial PCO_2 and internal jugular venous PO_2 in 4 men who breathed 100% O_2 and 2% CO_2 in O_2 at 3.5 ATA (22). In the transition from O_2 to O_2-CO_2, average arterial PCO_2 rose by 21 mm Hg from 37 to 58 mm Hg, with corresponding jugular venous PO_2 values of 76 and 1000 mm Hg, respectively. Although a comparable increment in brain venous PO_2 would not be expected during oxygen breathing at 2.0 ATA with an arterial PCO_2 elevation of 14 mm Hg at most, it is reasonable to predict that brain venous PO_2 would rise by several orders of magnitude.

The observation of consistent elevations in arterial PCO_2 during oxygen-exercise exposure at 2.0 ATA (Appendix Tables 10 and 16, Appendix Figures 5 and 6), in conjunction with the well documented relationship of cerebral blood flow to arterial PCO_2 (10,11), combine to focus attention on this finding as a potential cause of part or all of the apparently detrimental influence of exercise on CNS oxygen tolerance in man (1-4). Lambertsen et al (22) have previously suggested that exercise alone may not inherently reduce oxygen tolerance and that any associated decrement may be caused by the development of hypercapnia on an individual or situational basis. It is well established that some divers are individually predisposed to the development of hypercapnia during exercise (21), and that external factors such as excessive breathing resistance can have similar effects even in individuals who have normal CO_2 tolerance (21).

Potential for Development of Screening Procedures

The possibility that adverse influences of exercise on CNS oxygen tolerance can be linked to individual physiologic or behavioral factors that cause the development of hypercapnia during exercise has great operational significance. It is likely that such individuals could be identified by specific physiologic screening procedures that do not involve exposure to life-threatening conditions. It is also possible that patterns of intermittent oxygen exposure that are currently under investigation for practical and effective extension of oxygen tolerance in man at rest (Predictive Studies VI) could be directly applied to working divers in the absence of prominent hypercapnia during exercise. All of these potential benefits establish the requirement for investigation of the incidence and magnitude of arterial PCO_2 elevation under conditions that simulate actual working dives.

Preparations for Future Studies

Upon completing the measurements of physiological responses to exercise during oxygen exposure at 2.0 ATA under dry conditions, the final months of this Project period were used extensively to prepare for the proposed studies of oxygen-exercise interactions during underwater immersion. An Underwater Exercise Facility has been designed, and its construction within a vertically oriented compression chamber is nearly complete. The facility design allows the subject to remain submerged in a semi-reclining position while pedalling a bicycle ergometer whose control unit is above the subject and out of the water. Fiberglass flooring under and around the hyperbaric/hypobaric immersion pool allows access to the subject for investigators and instrumentation.

When the proposed study is adequately funded, the primary focus of investigation will be the quantitative determination of arterial PCO_2 in divers working under conditions that equal or exceed the stresses encountered in actual diving operations. In addition to the measurements obtained during underwater exercise, the same subjects will be studied while working at the same exercise levels during oxygen exposure at 2.0 ATA in the dry and also during air breathing at 1.0 ATA.

Investigation will focus upon measurement of ventilatory and arterial blood gas responses to 24 minutes of incremental work during air breathing at 1.0 ATA as a control state and during both dry and underwater oxygen exposure at 2.0 ATA. Corresponding responses to the same incremental workload during normoxic underwater exposure at 2.0 ATA will be measured as an additional control. If there are significant differences among the ventilatory and blood gas responses to the 4 sets of experimental conditions, this design will allow identification of which variables are most accountable (hyperoxia, increased gas density, or effects of immersion).

Recommendations for Immediate Implementation

Although additional studies are required to define more precisely the roles of oxygen in reducing respiratory response to exercise, and roles of arterial PCO_2 elevation in the detrimental influence of exercise on CNS oxygen tolerance, it is obvious that any external factors that increase the work of breathing during exercise while breathing oxygen can only augment the degree of hypercapnia beyond that found even under laboratory conditions that minimized resistance to breathing. Accordingly, it will be important to keep external breathing resistance as low as possible in any apparatus designed for use with hyperoxic gases. Potential exists in other investigations for developing methods of respiratory training to prevent arterial hypercapnia during exercise.

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EXTENSION OF CENTRAL NERVOUS AND VISUAL SYSTEM OXYGEN TOLERANCE IN PHYSICAL WORK

COMBINED FINAL REPORT

For

Contract Nos. N00014-88-K-0270 and N00014-88-K-0318

APPENDIX

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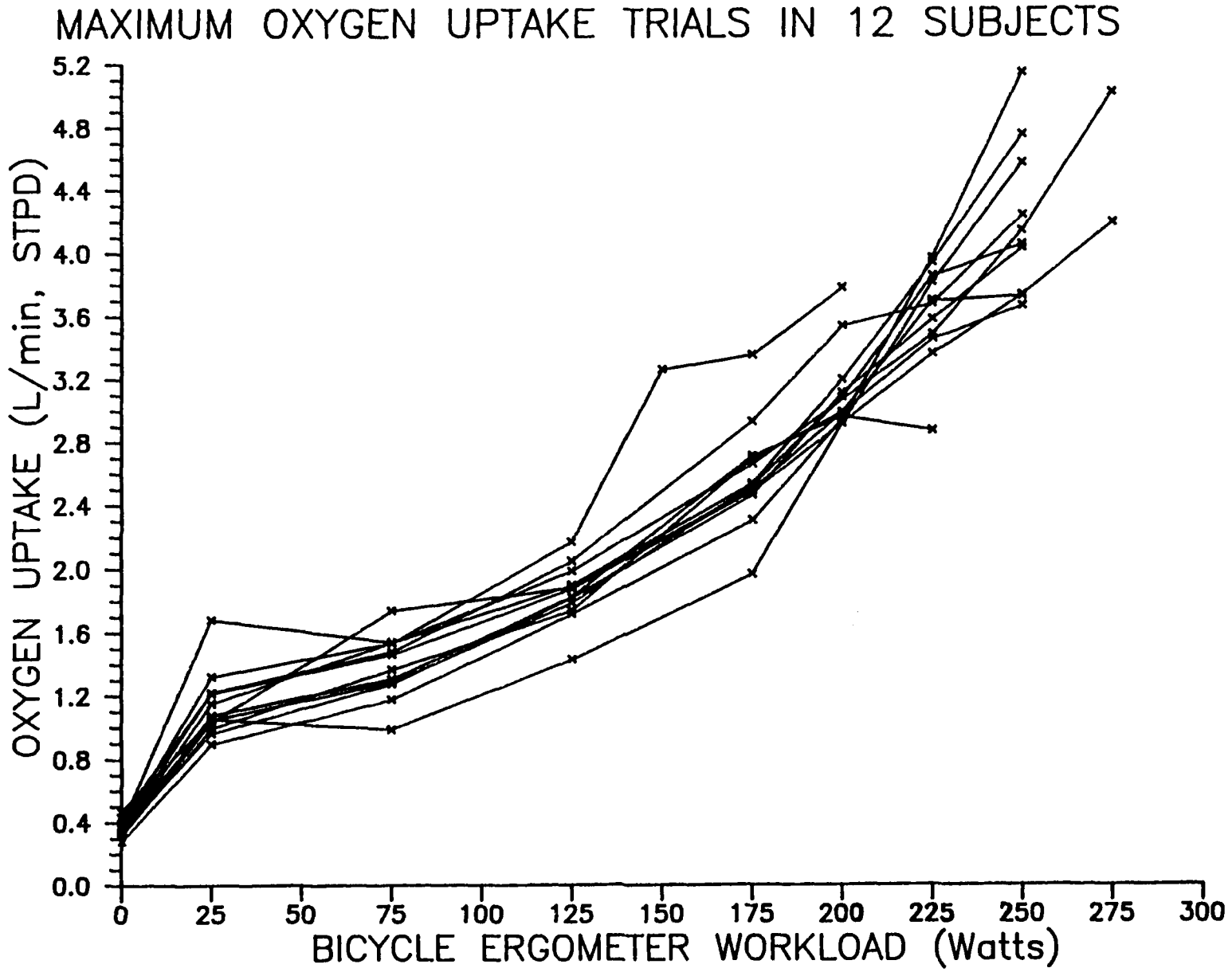
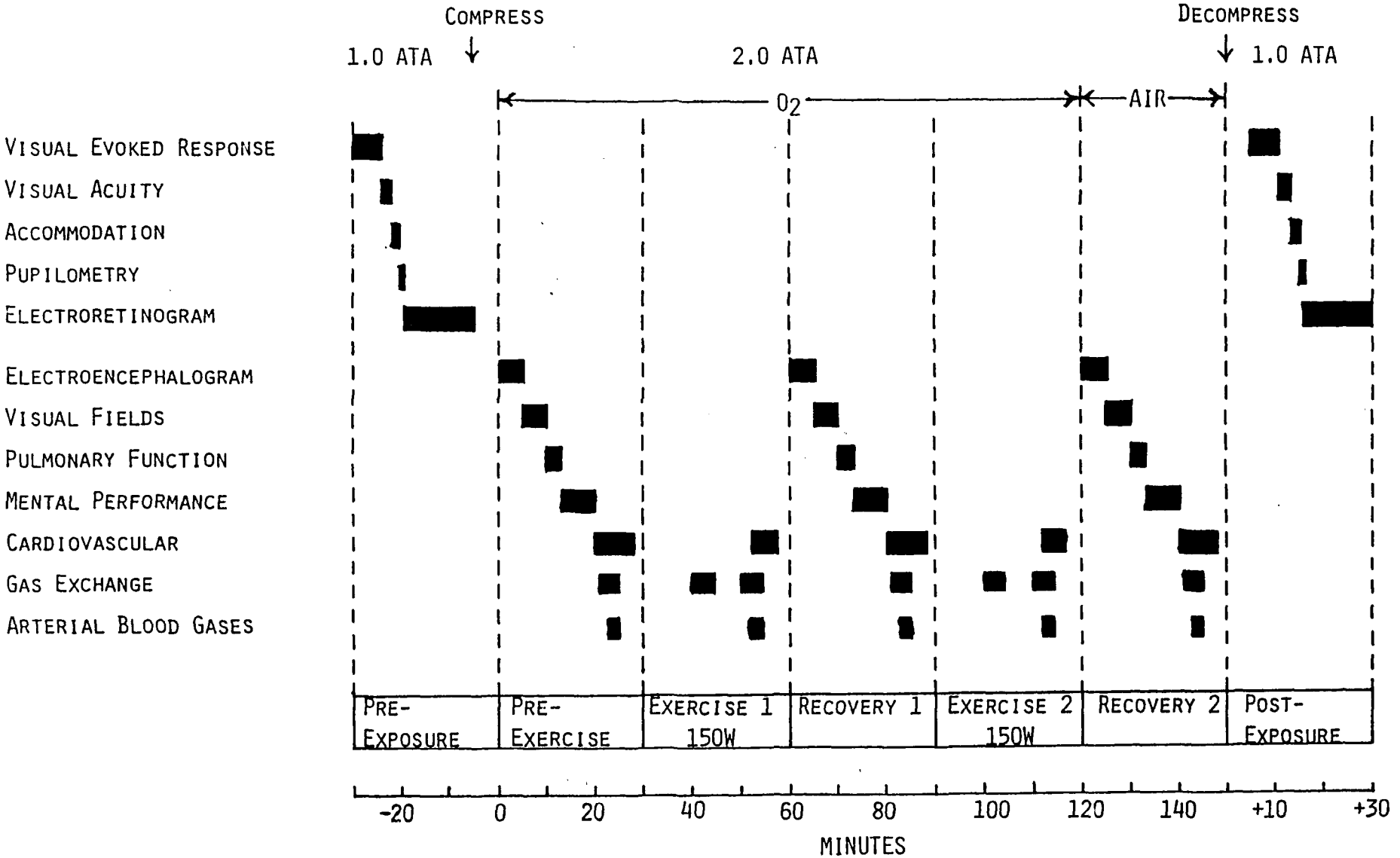
Appendix Figure 1



Appendix Figure 2

OXYGEN-EXERCISE INTERACTIONS AT 2.0 ATA
MEASUREMENT SEQUENCE - PROTOCOL 1

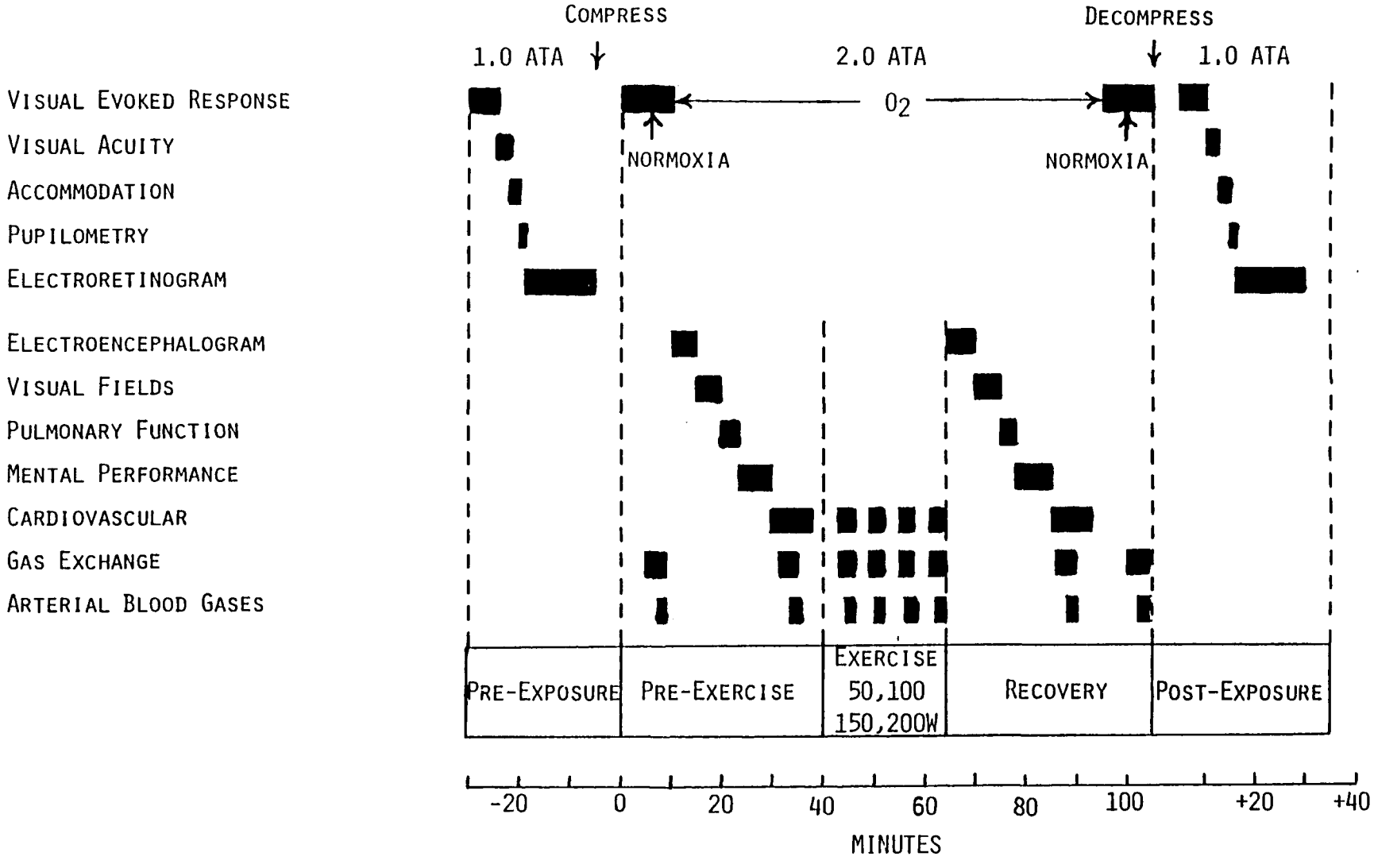
CONTINUOUS MONITORING: PULMONARY VENTILATION, END-TIDAL P_{CO_2}, MASK F_{O_2}, RECTAL TEMPERATURE



Appendix Figure 3

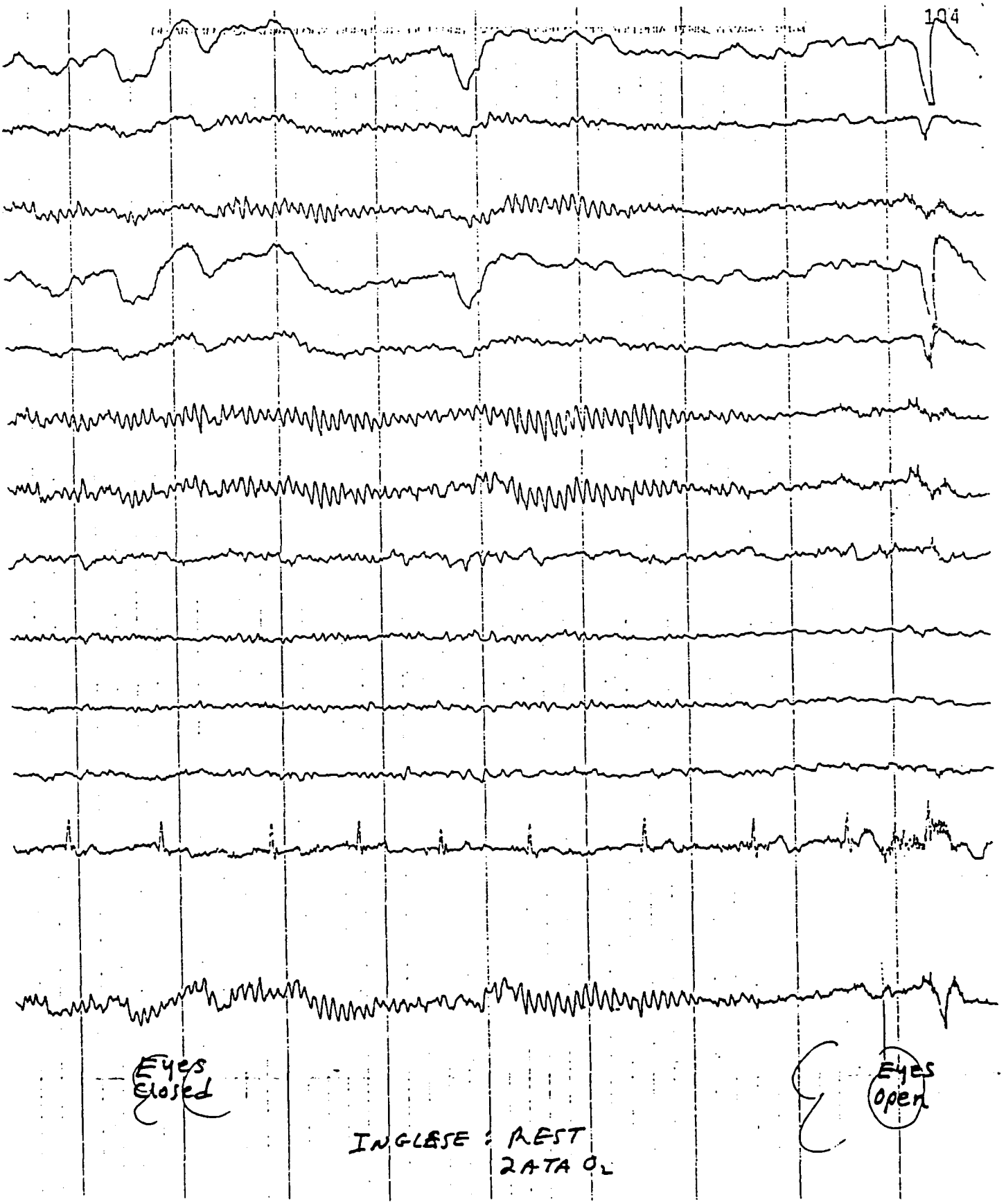
OXYGEN-EXERCISE INTERACTIONS AT 2.0 ATA
MEASUREMENT SEQUENCE - PROTOCOL 2

CONTINUOUS MONITORING: PULMONARY VENTILATION, END-TIDAL P_{CO_2}, MASK F_{O_2}, RECTAL TEMPERATURE



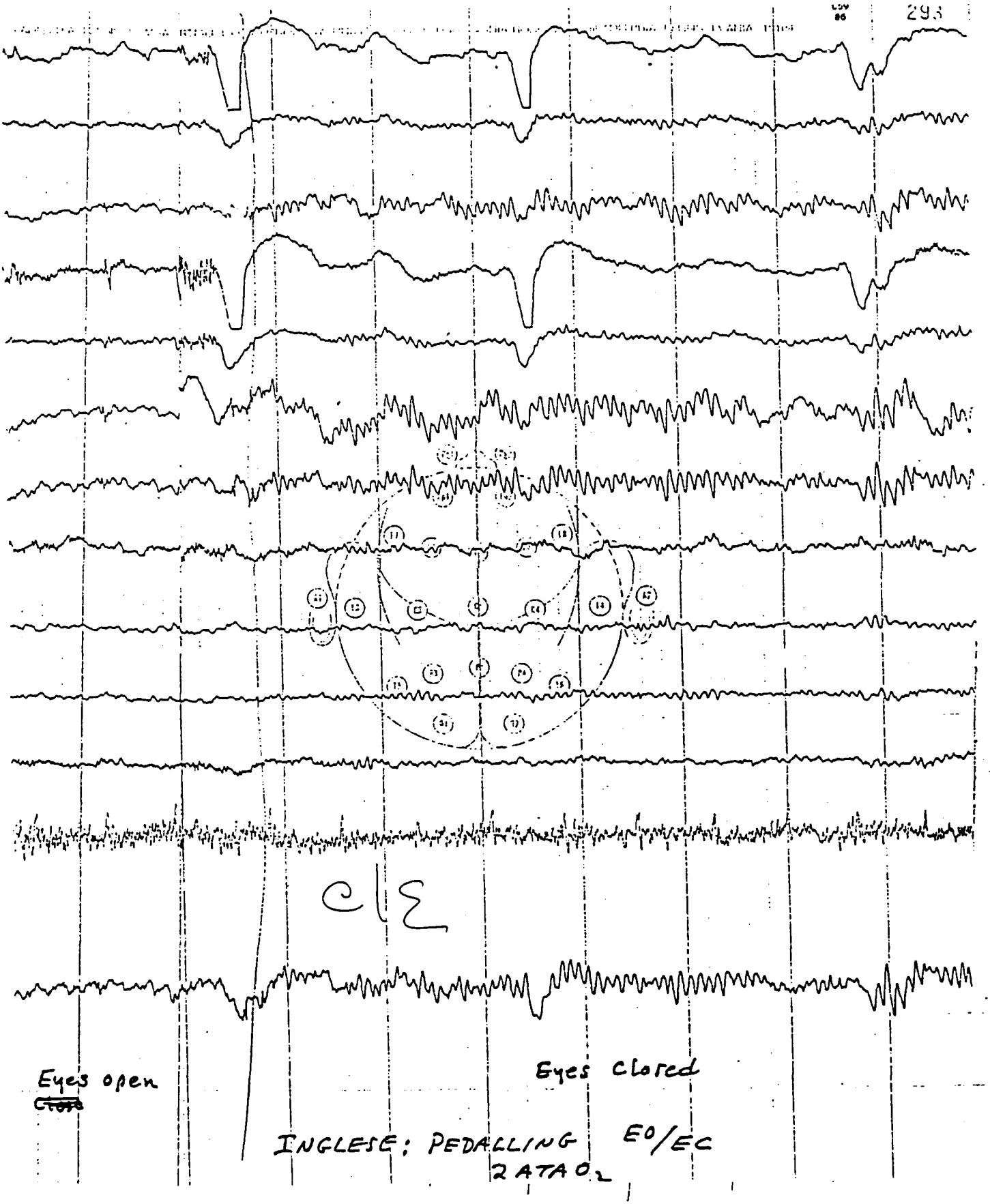
Appendix Figure 4A

EEG AT REST DURING OXYGEN BREATHING AT 2.0 ATA

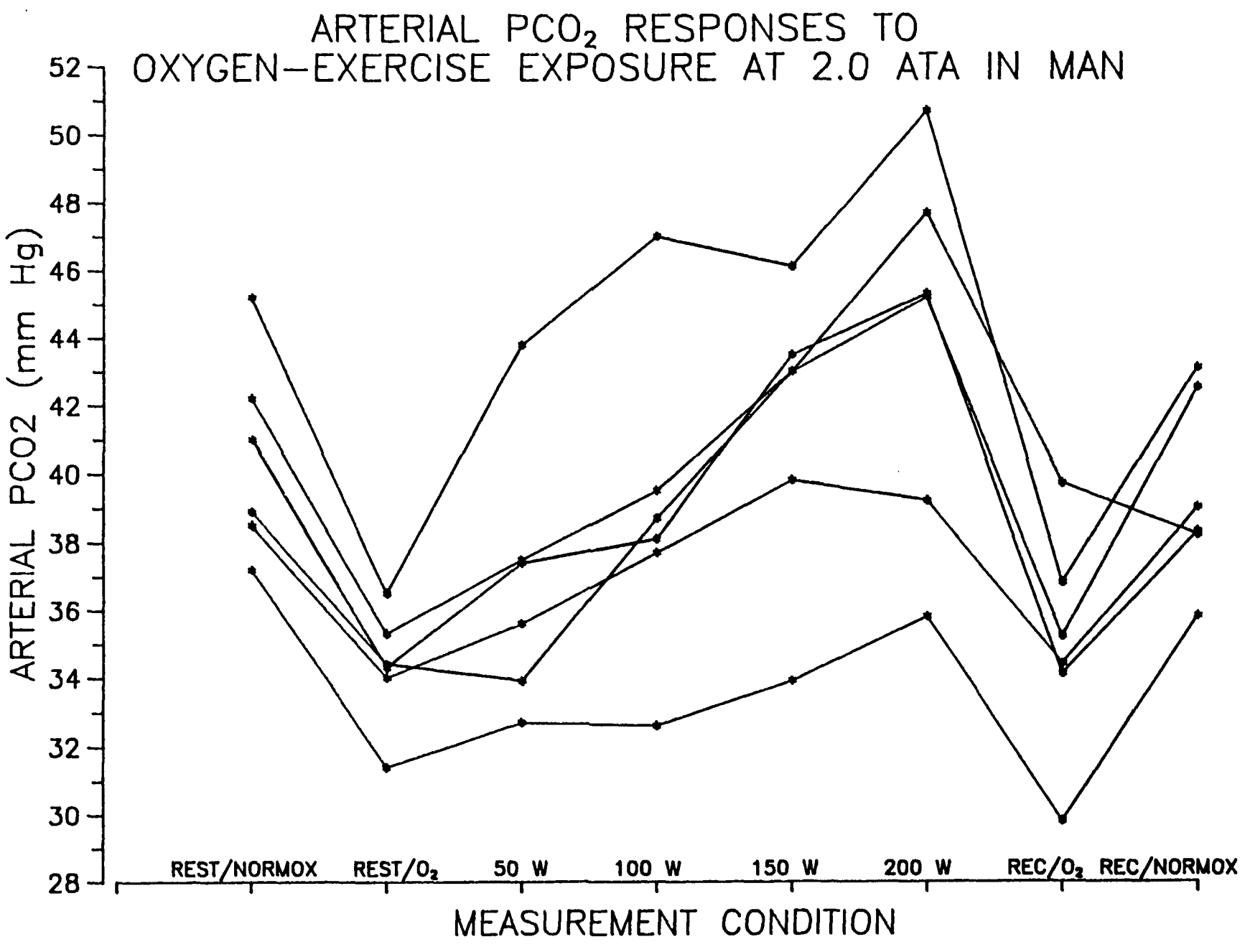


Appendix Figure 4B

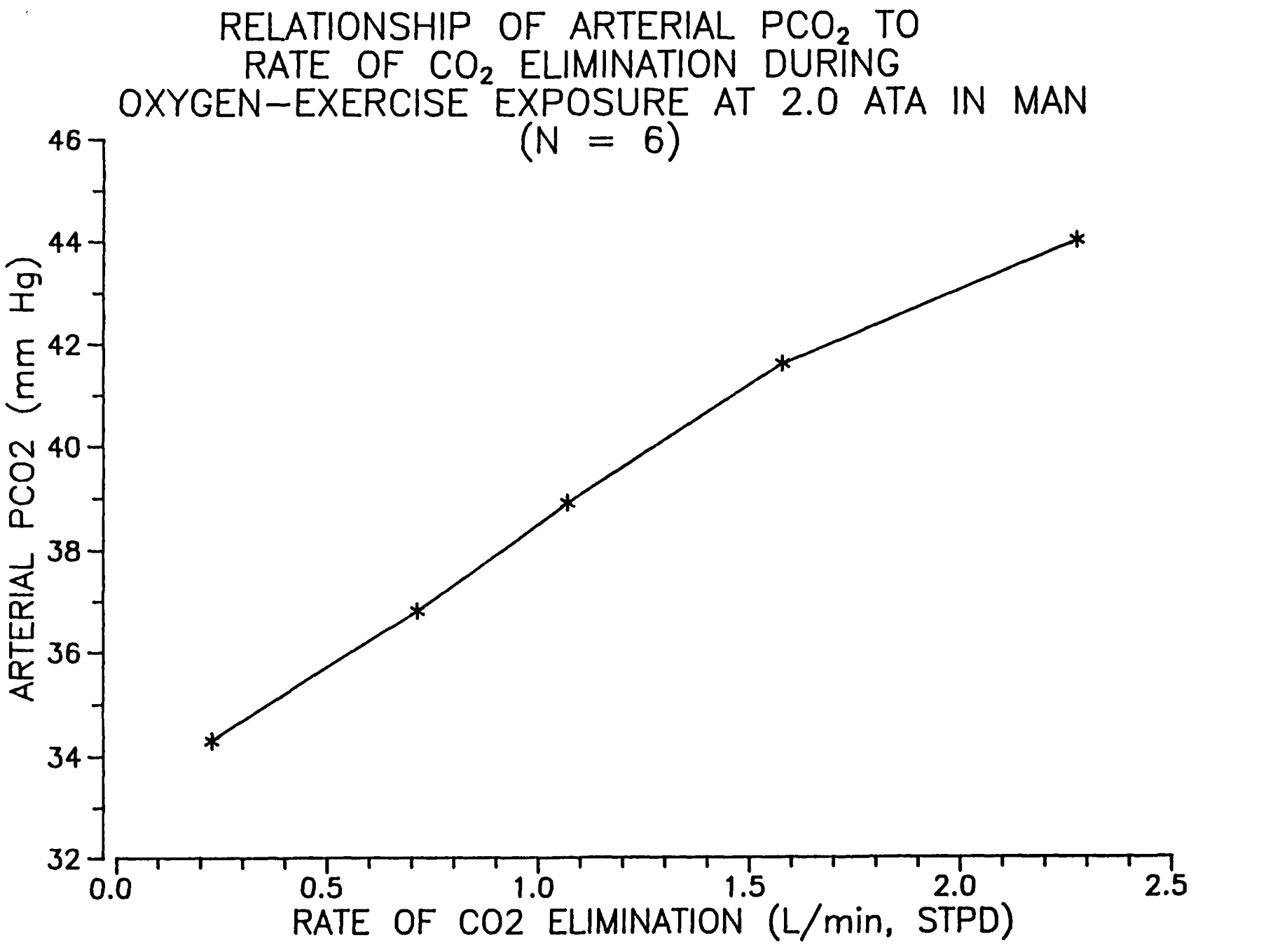
EEG DURING EXERCISE WHILE BREATHING OXYGEN AT 2.0 ATA



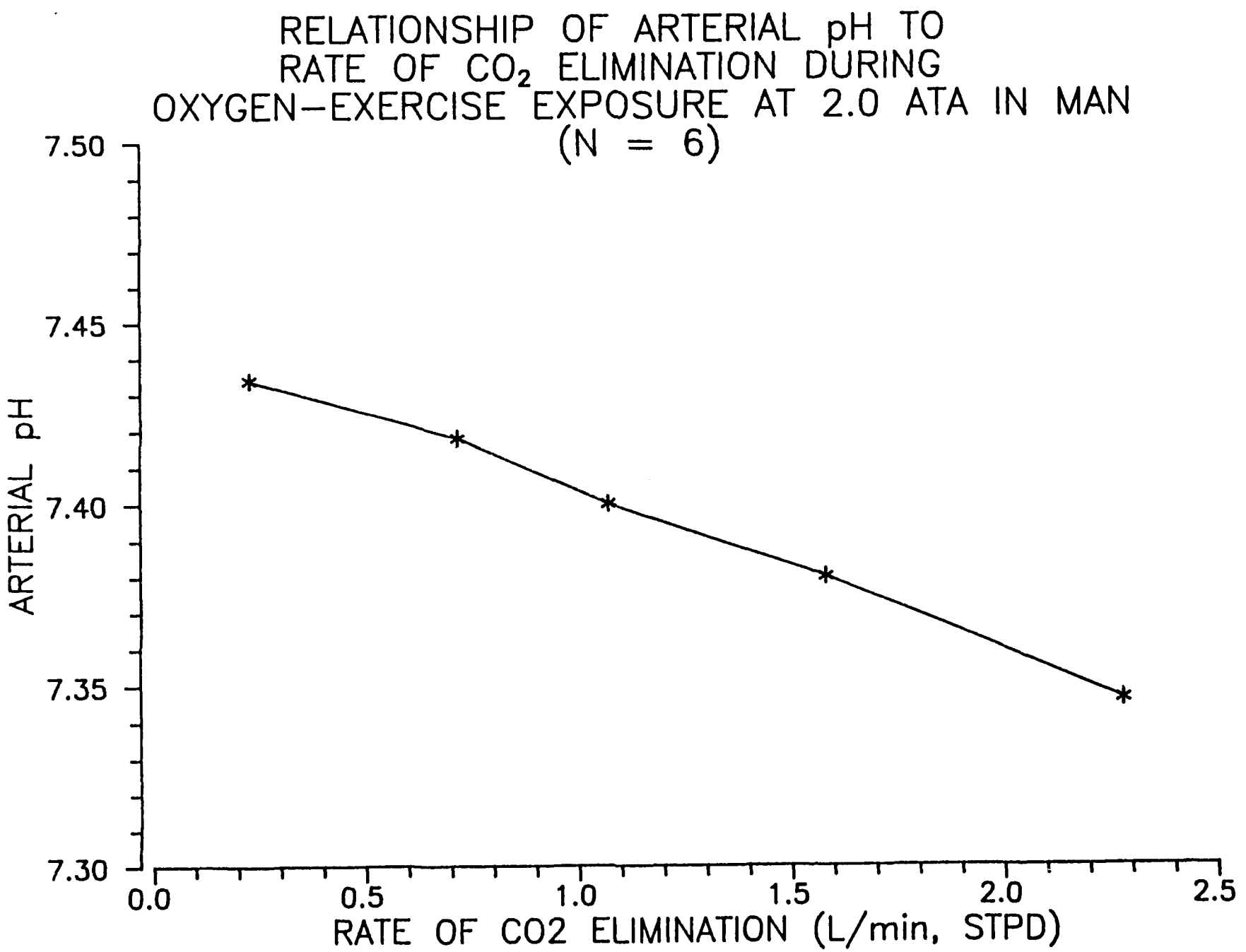
Appendix Figure 5



Appendix Figure 6



Appendix Figure 7



Appendix Table 1

EFFECTS OF INTERMITTENT EXERCISE ON MENTAL AND PSYCHOMOTOR FUNCTION DURING AIR BREATHING AT 1.0 ATA IN MAN

	Visual Digit Span (correct responses)	Key Insertion (correct responses)	Operations (correct-incorrect/3)	Visual Reaction Time (seconds)
Rest	33.8 ± 3.6(10)	53.1 ± 8.0(8)	44.0 ± 5.6(10)	0.269 ± 0.018(10)
Exercise 1				
Recovery 1	34.2 ± 7.5 (9)	53.4 ± 5.3(7)	45.0 ± 4.7 (9)	0.299 ± 0.078 (9)
Exercise 2				
Recovery 2	31.5 ± 7.5(10)	53.4 ± 8.1(8)	46.2 ± 4.5(10)	0.285 ± 0.039(10)

Mean ± S.D.(N)

Appendix Table 2

EFFECTS OF INTERMITTENT EXERCISE ON VISUAL FUNCTION DURING AIR BREATHING AT 1.0 ATA IN MAN

	Visual Acuity	Accommodation (Near-point, cm)	Pupil Diameter (mm)
Pre-Exposure	20/20	10.6 ± 1.7	3.9 ± 0.6
Rest			
Exercise 1			
Recovery 1			
Exercise 2			
Recovery 2			
Post-Exposure	20/20	11.1 ± 2.5	3.8 ± 0.5

	Electroretinogram (Amplitude, mV)	Visual Evoked Response (Latency, msec)	Visual Fields (Relative Area)
Pre-Exposure	328 ± 20	122 ± 12	
Rest			1.00
Exercise 1			
Recovery 1			1.00 ± 0.07
Exercise 2			
Recovery 2			0.97 ± 0.07
Post-Exposure	308 ± 30*	117 ± 10	

Mean ± S.D., N = 8

* Difference from pre-exposure statistically significant, $p \leq 0.05$.

Appendix Table 3

EFFECTS OF INTERMITTENT EXERCISE ON PULMONARY FUNCTION DURING AIR BREATHING AT 1.0 ATA IN MAN

	FVC (L)	FEV_1 (L)	PEFR (L/sec)	FEF_{25-75} (L/sec)
Rest	5.15 ± 0.83	4.30 ± 0.59	9.46 ± 1.63	4.67 ± 0.89
Exercise 1				
Recovery 1	5.22 ± 0.85	4.41 ± 0.57*	9.81 ± 1.62	4.88 ± 0.84
Exercise 2				
Recovery 2	5.22 ± 0.78	4.38 ± 0.59	9.47 ± 2.12	4.73 ± 0.97

Mean ± S.D., N = 10

* Difference from rest statistically significant, $p \leq 0.05$.

Appendix Table 4

EFFECTS OF INTERMITTENT EXERCISE ON VENTILATION AND GAS EXCHANGE DURING AIR BREATHING AT 1.0 ATA IN MAN

	$\dot{V}_E$ (L/min, BTPS)	V_T (L, BTPS)	f (br/min)
Rest	8.98 ± 1.26(10)	0.533 ± 0.098 (9)	16.9 ± 3.3 (9)
Exercise 1	54.56 ± 14.06(10)	1.708 ± 0.292 (9)	33.4 ± 9.2 (9)
Recovery 1	8.93 ± 1.69 (9)	0.536 ± 0.061 (8)	16.3 ± 2.3 (9)
Exercise 2	54.23 ± 14.45(10)	1.596 ± 0.207 (9)	35.0 ± 7.9 (9)
Recovery 2	8.77 ± 0.84 (9)	0.556 ± 0.073 (6)	16.9 ± 2.9 (9)

	$\dot{V}_{CO_2}$ (L/min, STPD)	$\dot{V}_{O_2}$ (L/min, STPD)	R
Rest	0.261 ± 0.042(10)	0.290 ± 0.039(10)	0.90 ± 0.13(10)
Exercise 1	1.841 ± 0.264(10)	1.868 ± 0.289(10)	0.99 ± 0.03(10)
Recovery 1	0.255 ± 0.064 (9)	0.303 ± 0.078(10)	0.80 ± 0.13(10)
Exercise 2	1.817 ± 0.304(10)	1.873 ± 0.284(10)	0.97 ± 0.04(10)
Recovery 2	0.251 ± 0.030 (9)	0.295 ± 0.059(10)	0.80 ± 0.10(10)

Mean ± S.D.(N)

Appendix Table 5

EFFECTS OF INTERMITTENT EXERCISE ON CARDIOVASCULAR FUNCTION AND CORE TEMPERATURE DURING AIR BREATHING AT 1.0 ATA IN MAN

	Heart Rate (beats/min)	Stroke Volume (ml)	Cardiac Output (L/min)
Pre-Exposure	67.1 ± 9.6[a]	114.6 ± 21.4[a]	7.65 ± 1.70[a]
Rest	58.9 ± 4.4	140.9 ± 44.5	8.30 ± 2.82
Exercise 1	144.6 ± 18.1	119.5 ± 25.7	17.23 ± 4.12
Recovery 1	76.1 ± 12.6	113.6 ± 24.5	8.47 ± 1.57
Exercise 2	151.1 ± 16.7	127.7 ± 29.6	19.39 ± 5.73
Recovery 2	78.5 ± 12.5	107.7 ± 35.4	8.27 ± 2.28

	Systolic B.P. (mm Hg)	Diastolic B.P. (mm Hg)	Core Temp (°C)
Pre-Exposure	124.9 ± 18.9[b]	74.5 ± 7.2[b]	37.0 ± 0.5[a]
Rest	122.8 ± 18.9	75.1 ± 9.3	37.0 ± 0.5
Exercise 1	161.7 ± 24.1	71.6 ± 13.6	37.6 ± 0.4
Recovery 1	123.0 ± 14.6	70.5 ± 11.7	37.5 ± 0.6
Exercise 2	157.5 ± 19.9	69.2 ± 13.7	37.9 ± 0.5
Recovery 2	121.7 ± 20.1	75.2 ± 9.7	37.6 ± 0.6

Mean ± S.D., N = 10, [a] N = 9, [b] N = 8

Appendix Table 6

EFFECTS OF INTERMITTENT EXERCISE ON MENTAL AND PSYCHOMOTOR FUNCTION DURING OXYGEN EXPOSURE AT 2.0 ATA IN MAN

	Visual Digit Span (correct responses)	Key Insertion (correct responses)	Operations (correct-incorrect/3)	Visual Reaction Time (seconds)
Rest/Air				
Rest/O2	35.7 ± 5.6	55.3 ± 10.7[a]	45.3 ± 5.4	0.275 ± 0.036
Exercise 1				
Recovery 1	37.0 ± 5.5	53.6 ± 8.9[a]	45.8 ± 5.1	0.280 ± 0.020
Exercise 2				
Rec.2/Air	34.2 ± 4.0	57.8 ± 6.5[a]	45.2 ± 5.2	0.279 ± 0.037

Mean ± S.D., N = 10, [a]N = 9

Appendix Table 7

EFFECTS OF INTERMITTENT EXERCISE ON VISUAL FUNCTION DURING AND AFTER OXYGEN EXPOSURE AT 2.0 ATA IN MAN

	Visual Acuity	Accommodation (Near-point, cm)	Pupil Diameter (mm)
Pre-Exposure	20/20	11.6 ± 1.9	3.8 ± 0.5
Rest/Air			
Rest/O_2			
Exercise 1			
Recovery 1			
Exercise 2			
Rec.2/Air			
Post-Exposure	20/20	11.6 ± 1.9	3.8 ± 0.4

	Electroretinogram (Amplitude, mV)	Visual Evoked Response (Latency, msec)	Visual Fields (Relative Area)
Pre-Exposure	327 ± 54	114 ± 6	
Rest/Air			
Rest/O_2			1.00
Exercise 1			
Recovery 1			0.99 ± 0.08
Exercise 2			
Rec.2/Air			0.99 ± 0.15
Post-Exposure	344 ± 72	110 ± 6	

Mean ± S.D., N = 10

Appendix Table 8

EFFECTS OF INTERMITTENT EXERCISE ON PULMONARY FUNCTION DURING AND AFTER OXYGEN EXPOSURE AT 2.0 ATA IN MAN

	FVC (L)	FEV_1 (L)	PEFR (L/sec)	FEF_{25-75} (L/sec)
Rest/Air				
Rest/O2	5.03 ± 0.80	3.67 ± 0.51	6.62 ± 0.82	3.08 ± 0.72
Exercise 1				
Recovery 1	5.15 ± 0.89*	3.73 ± 0.52	6.66 ± 1.43	3.13 ± 0.85
Exercise 2				
Rec. 2/Air	5.14 ± 0.89*	3.86 ± 0.52*	7.01 ± 1.41	3.41 ± 0.83*

Mean ± S.D., N = 10

* Difference from rest/O_2 statistically significant, $p \leq 0.05$.

Appendix Table 9

EFFECTS OF INTERMITTENT EXERCISE ON VENTILATION AND GAS EXCHANGE DURING OXYGEN EXPOSURE AT 2.0 ATA IN MAN

	$\dot{V}_E$ (L/min, BTPS)	V_T (L, BTPS)	f (br/min)	$\dot{V}_{CO_2}$ (L/min, STPD)
Rest/Air	8.12 ± 1.61[a]	0.644 ± 0.230[a]	14.0 ± 5.5[a]	0.243 ± 0.026[a]
Rest/O2	9.41 ± 2.26	0.608 ± 0.183	16.1 ± 4.1	0.229 ± 0.039
Exercise	52.44 ± 15.01	1.721 ± 0.292	30.4 ± 6.3	1.802 ± 0.456
Recovery	11.05 ± 1.58	0.625 ± 0.074	17.9 ± 3.5	0.272 ± 0.037
Exercise 2	51.96 ± 11.90	1.711 ± 0.190	30.4 ± 5.9	1.734 ± 0.323
Rec. 2/Air	9.72 ± 1.55	0.565 ± 0.088	17.6 ± 4.2	0.287 ± 0.040

Mean ± S.D., N = 10, [a] N = 7

Appendix Table 10

EFFECTS OF INTERMITTENT EXERCISE ON ARTERIAL PO_2, PCO_2, pH, AND $[HCO_3^-]$ DURING OXYGEN EXPOSURE AT 2.0 ATA IN MAN

	PO_2 (mmHg)	PCO_2 (mmHg)	pH	$[HCO_3^-]$ (meq/L)
Rest/Air	279 ± 41(6)	43.4 ± 5.7(7)	7.371 ± 0.025(7)	24.7 ± 2.8(7)
Rest/O_2	1306 ± 60(9)	38.1 ± 4.5(10) *	7.422 ± 0.033(10) *	24.5 ± 2.7(10)
Exercise 1	1305 ± 39(9)	43.3 ± 4.3(10) *	7.347 ± 0.067(10) *	23.4 ± 2.7(10)
Recovery 1	1324 ± 46(9)	38.3 ± 5.8(10) *	7.410 ± 0.044(10) *	23.8 ± 2.4(10)
Exercise 2	1324 ± 54(9)	42.8 ± 3.8(10) *	7.372 ± 0.043(10) *	24.4 ± 1.1(10)
Rec.2/Air	280 ± 31(9)	43.2 ± 4.4(10)	7.382 ± 0.034(10)	25.2 ± 1.8(10)

Mean ± S.D.(N)

* Statistically significant ($p \leq 0.05$) comparison between mean values determined by t-test adjusted for multiple comparisons following a significant F.

Appendix Table 11

EFFECTS OF INTERMITTENT EXERCISE ON CARDIOVASCULAR FUNCTION AND CORE TEMPERATURE DURING OXYGEN EXPOSURE AT 2.0 ATA IN MAN

	Heart Rate (beats/min)	Stroke Volume (ml)	Cardiac Output (L/min)
Pre-Exposure	59.6 ± 8.0(10)	121.3 ± 36.7(10)	7.12 ± 1.96(10)
Rest/Air	59.0 ± 7.6 (6)	140.3 ± 38.5 (6)	8.26 ± 2.60(6)
Rest/O_2	54.8 ± 4.5(10)	153.9 ± 36.4(10)	8.38 ± 1.91(10)
Exercise 1	129.2 ± 14.5(10)	132.1 ± 28.7(10)	17.00 ± 4.07(10)
Recovery 1	61.2 ± 10.0(10)	132.0 ± 38.1(10)	7.96 ± 2.26(10)
Exercise 2	134.8 ± 17.1(10)	136.2 ± 27.8(10)	18.40 ± 4.80(10)
Rec.2/Air	61.2 ± 11.9(10)	135.2 ± 41.8(10)	8.09 ± 2.23(10)

	Systolic B.P. (mm Hg)	Diastolic B.P. (mm Hg)	Core Temp (°C)
Pre-Exposure	142.1 ± 15.1(9)	70.4 ± 9.1(9)	36.9 ± 0.3(8)
Rest/Air	146.0 ± 17.5(6)	75.3 ± 13.5(6)	37.0 ± 0.4(5)
Rest/O_2	139.5 ± 11.2(10)	73.6 ± 10.3(10)	36.9 ± 0.3(10)
Exercise 1	169.8 ± 29.0(10)	72.7 ± 10.8(10)	37.3 ± 0.3(10)
Recovery 1	127.1 ± 8.6(10)	63.8 ± 5.4(10)	37.4 ± 0.3(10)
Exercise 2	160.3 ± 27.7(10)	73.1 ± 10.8(10)	37.6 ± 0.4(10)
Rec.2/Air	125.2 ± 8.4(10)	66.3 ± 9.5(10)	37.4 ± 0.5(10)

Mean ± S.D., (N)

Appendix Table 12

EFFECTS OF INCREMENTAL EXERCISE ON MENTAL AND PSYCHOMOTOR FUNCTION DURING OXYGEN EXPOSURE AT 2.0 ATA IN MAN

	Visual Digit Span (correct responses)	Key Insertion (correct responses)	Operations (correct-incorrect/3)	Visual Reaction Time (seconds)
Normoxia				
Rest/O2	37.3 ± 4.0	50.8 ± 10.1	45.3 ± 4.3	0.270 ± 0.029
Exercise-50				
Exercise-100				
Exercise-150				
Exercise-200				
Recovery/O_2	34.4 ± 3.1	52.6 ± 8.8	45.6 ± 4.6	0.268 ± 0.027
Normoxia				

Mean ± S.D., N = 8

Appendix Table 13

EFFECTS OF INCREMENTAL EXERCISE ON VISUAL FUNCTION DURING AND AFTER OXYGEN EXPOSURE AT 2.0 ATA IN MAN

	Visual Acuity	Accommodation (Near-point, cm)	Pupil Diameter (mm)
Pre-Exposure	20/20	11.4 ± 2.3	3.9 ± 1.0
Normoxia			
Rest/O_2			
Exercise-50			
Exercise-100			
Exercise-150			
Exercise-200			
Recovery/O_2			
Normoxia			
Post-Exposure	20/20	11.8 ± 2.4	3.9 ± 1.0

	Electroretinogram (Amplitude, mV)	Visual Evoked (Latency, msec)	Visual Fields (Relative Area)
Pre-Exposure	329 ± 44	112 ± 7	
Normoxia			
Rest/O_2			1.00
Exercise-50			
Exercise-100			
Exercise-150			
Exercise-200			
Recovery/O_2			1.01 ± 0.08[a]
Post-Exposure	346 ± 65	112 ± 8	

Mean ± S.D., N = 9, [a] N = 8

Appendix Table 14

EFFECTS OF INCREMENTAL EXERCISE ON PULMONARY FUNCTION DURING OXYGEN EXPOSURE AT 2.0 ATA IN MAN

	FVC (L)	FEV_1 (L)	PEFR (L/sec)	FEF_{25-75} (L/sec)
Normoxia				
Rest/O2	5.04 ± 0.84	3.66 ± 0.56	6.72 ± 0.46	3.00 ± 0.84
Exercise-50				
Exercise-100				
Exercise-150				
Exercise-200				
Recovery/O2	5.08 ± 0.92	3.71 ± 0.53	6.62 ± 0.66	3.16 ± 0.93
Normoxia				

Mean ± S.D., N = 9

Appendix Table 15

EFFECTS OF INCREMENTAL EXERCISE ON VENTILATION AND GAS EXCHANGE DURING OXYGEN EXPOSURE AT 2.0 ATA IN MAN

	$\dot{V}_E$ (L/min, BTPS)	V_T (L, BTPS)	f (br/min)	$\dot{V}_{CO_2}$ (L/min, STPD)
Normoxia	7.91 ± 1.61	0.583 ± 0.142	14.0 ± 2.8	0.211 ± 0.026
Rest/O_2	9.79 ± 1.63*	0.641 ± 0.147	15.7 ± 3.2	0.227 ± 0.038
Exercise-50	26.44 ± 4.58	1.261 ± 0.155	21.2 ± 3.9	0.786 ± 0.132
Exercise-100	36.66 ± 6.47	1.583 ± 0.122	23.2 ± 4.1	1.164 ± 0.176
Exercise-150	52.09 ± 10.49	1.873 ± 0.293	27.9 ± 3.8	1.785 ± 0.388
Exercise-200	75.60 ± 20.48	2.131 ± 0.315	35.4 ± 6.6	2.534 ± 0.456
Recovery/O_2	11.02 ± 2.29	0.603 ± 0.083	18.3 ± 3.0	0.243 ± 0.031
Normoxia	8.55 ± 2.35	0.566 ± 0.141	15.3 ± 3.2	0.217 ± 0.057

Mean ± S.D., N = 9

* Difference from normoxia statistically significant, $p \leq 0.05$.

Appendix Table 16

EFFECTS OF INCREMENTAL EXERCISE ON ARTERIAL PO_2, PCO_2, pH, AND $[HCO_3^-]$ DURING OXYGEN EXPOSURE AT 2.0 ATA IN MAN

	PO_2 (mmHg)	PCO_2 (mmHg)	pH	$[HCO_3^-]$ (meq/L)
Normoxia	124 ± 16	42.1 ± 4.7	7.381 ± 0.012	24.7 ± 2.6
Rest/O_2	1334 ± 44	36.5 ± 4.1	7.420 ± 0.031	23.4 ± 1.9
Exercise-50	1334 ± 34	39.4 ± 5.9	7.395 ± 0.047	23.6 ± 2.2
Exercise-100	1352 ± 37	41.2 ± 5.9	7.381 ± 0.041	24.0 ± 2.4
Exercise-150	1355 ± 36	42.7 ± 3.9	7.354 ± 0.052	23.4 ± 2.6
Exercise-200	1327 ± 44[a]	42.7 ± 5.2	7.313 ± 0.075	21.5 ± 4.3
Recovery/O_2	1329 ± 71[a]	36.6 ± 4.4	7.405 ± 0.064	22.6 ± 2.5
Normoxia	126 ± 25	40.9 ± 3.4	7.382 ± 0.037	24.0 ± 2.2

Mean ± S.D., N = 9, [a] N = 8

Appendix Table 17

EFFECTS OF INCREMENTAL EXERCISE ON CARDIOVASCULAR FUNCTION AND CORE TEMPERATURE DURING OXYGEN EXPOSURE AT 2.0 ATA IN MAN

	Heart Rate (beats/min)	Stroke Volume (ml)	Cardiac Output (L/min)
Pre-Exposure	60.3 ± 7.5(9)	117.0 ± 22.0(9)	7.02 ± 1.44(9)
Normoxia	56.0 ± 6.7(9)	153.3 ± 50.9(9)	8.47 ± 2.72(9)
Rest/O_2	48.8 ± 6.8(8)	163.9 ± 46.2(8)	7.94 ± 2.27(8)
Exercise-50	78.9 ± 7.4(8)	159.6 ± 71.6(8)	12.55 ± 5.51(8)
Exercise-100	94.1 ± 9.8(8) *	151.6 ± 49.4(8) *	14.48 ± 5.45(8) *
Exercise-150	118.4 ± 15.1(8)	140.6 ± 49.7(8)	16.74 ± 6.53(8)
Exercise-200	139.9 ± 17.5(8)	114.0 ± 37.5(8)	16.36 ± 7.28(8)
Recovery/O_2	64.6 ± 9.8(9)	135.7 ± 32.8(9)	8.68 ± 2.31(9)
Normoxia	66.0 ± 8.5(9)	123.8 ± 27.5(9)	8.06 ± 1.60(9)

	Systolic B.P. (mm Hg)	Diastolic B.P. (mm Hg)	Core Temp (°C)
Pre-Exposure	137.7 ± 15.9(9)	72.9 ± 5.8(9)	36.8 ± 0.2(9)
Normoxia	138.9 ± 11.6(9)	69.4 ± 6.5(9)	36.7 ± 0.2(9)
Rest/O_2	141.4 ± 10.5(9)	74.0 ± 7.8(9)	36.8 ± 0.2(9)
Exercise-50	156.3 ± 19.6(9)	70.9 ± 13.0(9)	36.8 ± 0.3(9)
Exercise-100	162.8 ± 20.7(9) *	73.3 ± 13.1(9) *	36.8 ± 0.3(9) *
Exercise-150	183.4 ± 22.5(9)	77.4 ± 12.2(9)	36.9 ± 0.2(9)
Exercise-200	195.1 ± 27.3(9)	82.1 ± 12.1(9)	37.1 ± 0.2(9)
Recovery/O_2	132.8 ± 11.3(9)	70.3 ± 6.7(9)	37.3 ± 0.3(9)
Normoxia	132.2 ± 8.8(9)	72.0 ± 9.1(9)	37.2 ± 0.3(9)

Mean ± S.D.(N)
* Statistically significant ($p \leq 0.05$) trend across increasing work loads.

Appendix Table 18

EFFECTS OF INTERMITTENT EXERCISE ON VENTILATION AND GAS EXCHANGE.
MEASUREMENTS DURING OXYGEN EXPOSURE
AT 2.0 ATA COMPARED WITH AIR AT 1.0 ATA.
Mean values in 7 men.

	$\dot{V}_E$ (L/min, BTPS)		V_T (L, BTPS)		f (br/min)		$\dot{V}_{CO_2}$ (L/min, STPD)	
	1 ATA Air	2 ATA O_2	1 ATA Air	2 ATA O_2	1 ATA Air	2 ATA O_2	1 ATA Air	2 ATA O_2
Rest	8.99	10.18	0.570	0.670*	16.0	16.1	0.266	0.244
Exercise 1	53.31	53.16	1.774	1.806*	30.6	29.6	1.894	1.814
Recovery 1	8.53	11.21	0.551	0.627*	15.5	18.2	0.249	0.277
Exercise 2	54.27	52.28	1.630	1.756*	33.4	29.9*	1.878	1.719*
Recovery 2	8.82	10.05	0.552	0.597*	16.3	17.3	0.253	0.302

* Significant differences across O_2 pressure at each exercise level, $p \leq 0.05$. Individual comparison made following ANOVA regardless of significance of overall effect.

Appendix Table 19

EFFECTS OF INCREMENTAL EXERCISE ON VENTILATION AND GAS EXCHANGE DURING OXYGEN EXPOSURE AT 2.0 ATA IN MAN (SUBJECTS WHO COMPLETED ALL WORK LOADS)

	$\dot{V}_E$ (L/min, BTPS)	V_T (L, BTPS)	f (br/min)	$\dot{V}_{CO_2}$ (L/min, STPD)
Normoxia	8.02 ± 1.75	0.586 ± 0.169	14.3 ± 3.4	0.204 ± 0.026
Rest/O_2	10.30 ± 1.33	0.674 ± 0.174	15.9 ± 3.3	0.226 ± 0.048
Exercise-50	25.95 ± 3.45	1.213 ± 0.158	21.8 ± 4.3	0.713 ± 0.033
Exercise-100	36.33 ± 4.90 *	1.549 ± 0.137 *	23.6 ± 3.7 *	1.069 ± 0.062 *
Exercise-150	48.46 ± 5.96	1.736 ± 0.216	28.2 ± 4.0	1.578 ± 0.075
Exercise-200	66.09 ± 9.77	2.051 ± 0.259	32.6 ± 5.6	2.276 ± 0.155
Recovery/O_2	11.69 ± 1.90	0.604 ± 0.103	19.5 ± 2.0	0.245 ± 0.034
Normoxia	8.12 ± 0.89	0.504 ± 0.066	16.4 ± 3.1	0.197 ± 0.029

Mean ± S.D., N = 6

* Statistically significant ($p \leq 0.05$) trend across increasing work loads.

pendix Table 20

NTAL EXERCISE ON ARTERIAL PO_2, PCO_2
UR[illegible]NC OXYGEN EXPOSURE AT 2.0 ATA
O COMPLETED ALL WORK LOADS)

PCO_2 (mmHg)	pH	$[HCO_3^-]$ (meq/L)
40.5 ± 2.9	7.384 ± 0.012	23.9 ± 2.2
4.3 ± 1.7	7.434 ± 0.025	22.9 ± 2.1
36.8 ± 3.9	7.418 ± 0.028	23.5 ± 2.5
8.9 ± 4.6 *	7.400 ± 0.027 *	23.9 ± 2.8
1.6 ± 4.2	7.380 ± 0.022	24.2 ± 2.5
44.0 ± 5.5	7.346 ± 0.029	23.6 ± 2.6
5.0 ± 3.3	7.436 ± 0.035	23.4 ± 2.2
39.5 ± 2.8	7.400 ± 0.022	24.2 ± 2.5

p ≤ 0.05) trend across increasing

1

ARDIOVASCULAR FUNCTION
)SURE AT 2.0 ATA
..0 ATA
men

Volume (l) 2 ATA O_2	Cardiac Output (L/min) 1 ATA Air	Cardiac Output (L/min) 2 ATA O_2
153.9	8.30	8.38
132.1	17.23	17.00
132.0	8.47	7.96
136.2	19.39	18.40
135.2*	8.27	8.09

ssure at each exercise
ison made following ANOVA
ll effect.

1 July 1990

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